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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LI, QIAN JANICE	
ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 11/02/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/857,325	ELLIOTT ET AL.	
	Examiner	Art Unit	
	Q. Janice Li, M.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 August 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *181-192,194-205 and 212-221* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *212-215* is/are allowed.

6)☒ Claim(s) *181-188, 190, 191,194-200, 202-204, 216-218, 221* is/are rejected.

7)☒ Claim(s) *189,192,201,205,219 and 220* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/7/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment and response submitted on 8/11/05 have been entered. Claims 110-180, 193, 206-211 have been canceled. Claims 212-221 are newly submitted. Claims 181-192, 194-205, and 212-221 are pending and under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims will not be reiterated. The arguments in 8/11/05 response would be addressed to the extent that they apply to current rejections.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 181, 182, 184, 186 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Rayat et al* (Diabetes 1998;47:1406-11) and *Nielsen et al* (US 6,225,310), and further in view of *Boss et al* (US 6,432,710) and *Champion et al* (US 4,850,993), for reasons of record.

Claim 183 stands rejected under 35 U.S.C. 103(a) as being unpatentable over *Rayat et al* (Diabetes 1998;47:1406-11) in view of *Nielsen et al* (US 6,225,310), *Boss et al* (US 6,432,710) and *Champion et al* (US 4,850,993), as applied to claims 181, 182, 184, 186 above, and further in view of *Brandhorst et al* (Transplant 1999;68:355-61, IDS), for reasons of record.

Claims 185 and 190 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Rayat et al* (Diabetes 1998;47:1406-11) in view of *Nielsen et al* (US 6,225,310), *Boss et al* (US 6,432,710) and *Champion et al* (US 4,850,993), as applied to claims 181, 182, 184, 186 above, and further in view of *Clark et al* (Endocrinol 1990;126:1895-1903) and *Maysinger et al* (CA 2,216,055, IDS), for reasons of record.

Claims 187 and 188 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Rayat et al* (Diabetes 1998;47:1406-11) in view of *Nielsen et al* (US 6,225,310), *Boss et al* (US 6,432,710), and *Champion et al* (US 4,850,993), as applied to claims 181, 182, 184, 186 above, and further in view of *Pu et al* (Brit J Pharmacol 1996;118:1072-8), for reasons of record.

Claims 190 and 191 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Rayat et al* (Diabetes 1998;47:1406-11) in view of *Nielsen et al* (US 6,225,310), *Boss et al* (US 6,432,710), and *Champion et al* (US 4,850,993), as applied to claims 181, 182, 184, 186 above, and further in view of *Saura et al* (Neuroendocrinol 1999 Jan 18;161-4).

Claims 194, 195, 197 stand rejected under 35 U.S.C. 103(a) as being obvious over *Rayat et al* (Diabetes 1998;47:1406-11), in view of *Nielsen et al* (US 6,225,310), for reasons of record.

Claim 196 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Rayat et al* (Diabetes 1998;47:1406-11), and *Nielsen et al* (US 6,225,310) as applied to claims 194, 195, 197 above, and further in view of *Brandhorst et al* (Transplant 1999;68:355-61, IDS), for reasons of record.

Claims 198 and 202 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Rayat et al* (Diabetes 1998;47:1406-11) and *Nielsen et al* (US 6,225,310) as applied to claims 194, 195, and 197 above, and further in view of *Clark et al* (Endocrinol 1990;126:1895-1903) and *Maysinger et al* (CA 2,216,055, IDS), for reasons of record.

Claims 202 and 203 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Rayat et al* (Diabetes 1998;47:1406-11), *Nielsen et al* (US 6,225,310), *Clark et al* (Endocrinol 1990;126:1895-1903) and *Maysinger et al* (CA 2,216,055, IDS) as applied to claims 194, 195, 197, 198, 202 above, and further in view of *Saura et al* (Neuroendocrinol 1999 Jan 18;161-4); for reasons of record.

Claims 199, 200 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Rayat et al* (Diabetes 1998;47:1406-11) and *Nielsen et al* (US 6,225,310), as applied to claims 194, 195, and 197 above, and further in view of *Pu et al* (Brit J Pharmacol 1996;118:1072-8), for reasons of record.

Claim 204 stands rejected under 35 U.S.C. 103(a) as being unpatentable over *Rayat et al* (Diabetes 1998;47:1406-11) and *Nielsen et al* (US 6,225,310), as applied to claims 194, 195, and 197 above, and further in view of *Boss et al* (US 6,432,710) and *Champion et al* (US 4,850,993), for reasons of record.

Applicants addressed the above rejections together generally and each cited references individually. The arguments will be addressed below.

Applicants first allege that the Office has improperly relied upon a total of eleven references collected in various combinations to form the bases for nine separate § 103 rejections, and each rejection represents a random combination of three or five disparate references.

In response, for the record, six references are relied upon formulating eleven separate rejections, and address more than 11 limitations. Other references are on record as evidence to support certain Official Notice. The references are combined according to the limitations recited in each of the claims. If applicants insist the references are randomly combined, it is because the limitations in the pending claims appear at times to be randomly combined. Moreover, in response to applicant's implication that the examiner has combined an excessive number of references, reliance on a large number of references in a rejection does not, without more, weigh against the obviousness of the claimed invention. See *In re Gorman*, 933 F.2d 982, 18 USPQ2d 1885 (Fed. Cir. 1991).

Applicants then present general arguments with respect to whether there was any motivation to combine and whether there was reasonable expectation of success.

In response, the rejections not only addressed each of the limitations in the claims, but also pointed to the motivation to combine and why there is a reasonable expectation of success. The details of each rejection have been on record, and will be further addressed below. Concerning applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). Additionally,

the court has determined that finding obviousness does not require expressly written motivation to combine in prior art since the motivation to combine may be found in the nature of the problem to be solved. "FINDING OF OBVIOUSNESS DOES NOT REQUIRE EXISTENCE OF EXPRESS, WRITTEN MOTIVATION TO COMBINE IN PRIOR ART, SINCE MOTIVATION TO COMBINE MAY BE FOUND IN NATURE OF PROBLEM TO BE SOLVED, LEADING INVENTORS TO LOOK TO REFERENCES RELATING TO POSSIBLE SOLUTIONS TO THAT PROBLEM". (*Ruiz v. A.B. Chance Co.*, 69 USPQ2d 1686 CA FC 2004).

The arguments to each cited reference are addressed below.

(1) Rayat et al.

Applicants first note that *Rayat* reference doesn't even mention BSA as a "trauma-protecting agent". In response, this issue has been explained in the first action on merit (page 7 of the Office action mailed 7/20/03), which states:

> The specification fails to define the trauma-protecting agent, thus, any agent that promote cell growth and suppress apoptosis would be considered as meeting the claim limitation.

To this end, it is well known in the art BSA qualifies as a trauma-protecting agent. For example, *Tsay et al* (USP 5,561,108) teach that "Plasma Protein Fraction and albumin are useful in treatment of shock due to burns, crushing injuries, abdominal emergencies, and any other trauma producing a predominant loss of plasma fluids but not red cells;" (column 1, lines 51-55). It is also noted that applicants have not challenged the assertion prior to this response, and current challenge was not proper since it was

not supported by evidence to the contrary. Nevertheless, the support for the previous Official Notice has been set forth *supra*.

Applicants then asserted that the reference does not teach or suggest a class of anesthetic agents is useful in the process for preparation of porcine islets. In response, applicants are reminded that the rejection of claims drawn to using anesthetic agents is not relied on Rayat reference alone, but combined with other references, particularly in view of *Pu et al*. Accordingly, the rejection relied on Rayat reference is proper.

(2) Elliott et al.

There are several references cited in the prosecution history are authored by Elliott, none of them are relied on under § 103 currently.

The only Elliott et al reference still standing is the US patent 6,146,653 under double patenting rejection. Applicants indicated that the patent is commonly owned, and a declaration under § 1.131 is sufficient to remove as prior art. However, since the rejection is under double patenting section, only terminal disclaimer could obviate the rejection.

There is an Elliott reference (Ann NY Acad Sci 1993) under 103 section, that was cited as evidence, not the basis for rejection.

(3) Brandhorst et al.

(4) Clark et al.

(5) Maysinger et al.

These references are part of the basis for rejecting claim limitations associated with the use of liberase in place of collagenase, and including IGF and HAS in the culture medium for islet cells.

Applicants allege that the Office action is improper and a clear example of hindsight reconstruction, and the standard is whether or not one would have motivation to modify the teachings of the prior art, and achieve the claimed results.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In the instant case, the reasoning is entirely based on the knowledge at the time before the invention was made. Moreover, the motivation to combine references may be found in the nature of the problem to be solved.

For example, *Brandhorst et al* teach that a barrier for successful islet isolation is the intrinsic fragility of islets during pancreas digestion and using human Liberase could **double** the yield of islet cells compared to collagenase (abstract). Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by *Rayat et al* and *Nielsen et a* by simply substituting collagenase with Liberase in pancreas harvesting and digestion as taught by *Brandhorst*

et al with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because it could enhance the yields of islet cells substantially. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Clark et al and *Maysinger et al* teach the need for developing a defined medium and the function of the components in the medium for long term sustained culture of mammalian islet cells, which comprising IGF-I and HAS for culturing islet cells of rats long before the effective filing date. These references established that IGF-I and HAS are well-known components for culturing pancreatic islet cells. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by *Rayat et al, Nielsen et al*, *Clark et al*, and *Maysinger et al* by simply including IGF-I and HAS and adding trauma protecting agent during the mechanical disassociation of pancreas with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because the modified method enhances the viability and sustained survival of ex vivo cultured islet cells. Given the success as established by *Clark et al*, and *Maysinger et al*, one would have had a reasonable expectation of success. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

(6) Saura et al.

Applicants argue *Saura et al* teach that GPE has the activity of IGF-1 in brain tissue, such knowledge would not obviously lead one of skill in the art for using such in preparing islet cells.

In response, a skilled artisan reading the teaching of *Saura et al* will not limit the teaching to brain cells, because *Saura et al* teach the GPE is a naturally occurring fragment of the IGF-1, and IGF-1 is believed to undergo N-terminal cleavage by a specific protease for its function. Thus, as long as the receptor for IGF-1 is present in brain cells and islet cells (as shown by Clark et al for example), it is reasonable to predict that GPE would also function in islet tissue as does the IGF-1 in both brain and islet tissue. Since IGF-1 functions in both islet cells and brain cells, there is a reasonable expectation of success when substituting IGF-1 with GPE given the confirmation provided by *Saura et al* in the absence of evidence to the contrary. Note that obviousness does not require absolute predictability of success; for obviousness under 35 U.S.C. § 103, all that is required is a reasonable expectation of success. See In re O'Farrell, 7 USPQ2d 1673 (CAFC 1988).

(7) Pu et al.

Applicants are reminded that the Office has accepted applicant's assertion that culturing the pig islets with lignocaine unexpectedly increased the viability of the pig islets by six-fold. Thus, once the claims are limited to lignocaine, the Pu et al reference will no longer apply. However, claims 187, 188, 199, 200, and new claims 216-218 encompass any anaethetic agent, and any phospolipase A2 inhibitor, the alleged unexpected results do not apply to the broadly claimed agents. The court has determined, "WHETHER THE UNEXPECTED RESULTS ARE THE RESULT OF UNEXPECTEDLY IMPROVED RESULTS OR A PROPERTY NOT TAUGHT BY THE PRIOR ART, THE "OBJECTIVE EVIDENCE OF NONOBVIOUSNESS MUST BE COMMENSURATE IN SCOPE WITH THE CLAIMS WHICH THE EVIDENCE IS OFFERED TO SUPPORT." IN OTHER WORDS, THE SHOWING OF UNEXPECTED RESULTS MUST BE

REVIEWED TO SEE IF THE RESULTS OCCUR OVER THE ENTIRE CLAIMED RANGE. *IN RE CLEMENS*, 622 F.2D 1029, 1036, 206 USPQ 289, 296 (CCPA 1980)" ((MPEP 716.02(d), emphasis added)). Neither the art of record nor the specification teaches the genus of anesthetic agents, can achieve the unexpected results, the scope of the rejected claims are not commensurate in scope with the evidence offered. Accordingly, for reasons of record and set forth *supra*, the claimed invention remains obvious over *Rayat et al* in view of *Nielsen et al, Boss et al* and *Champion et al*; and further in view of *Pu et al*.

Applicants assert the knowledge that lignocaine can act to restore heart contractions would suggest nothing to one of skill in the art about isolating pancreatic islet cells.

In response, as an initial matter, the contractibility of heart cells is a measurement for health status of these cells, even though such status in pancreatic beta cells is not measured by the contraction, the protective effect on myocytes reflects general beneficial effect of lignocaine. *Pu et al* have extend the observation of lignocaine in protecting heart cells to apply to all tissue recovery from minor trauma, and the trauma due to tissue harvesting and extraction certainly fall within the category of minor trauma. *Pu et al* suggested that although further confirmation study is needed, lignocaine is likely a promising therapeutic intervention (abstract, § 5). Thus, in the absence of evidence to the contrary, an expectation of success is reasonable. Note that obviousness does not require absolute predictability of success; for obviousness under 35 U.S.C. § 103, all that is required is a reasonable expectation of success. See In re O'Farrell, 7 USPQ2d 1673 (CAFC 1988).

(8) Boss et al.

(9) Champion et al

Applicants argue that Boss et al teach tylosin, which is a non-quinolone antibiotic. In response, Applicant's attention is directed to column 13, line 55 of the '710 patent, where ciprofloxacin is listed in the same markush group as tylosin. Thus, *Boss et al* clearly teach quinolone antibiotics exemplified by ciprofloxacin.

It is also noted for the record, the claims as original written recites "quinaline" and "ciproxin" and later changed to quinolone, and ciprofloxacin, and quinoline appears to be a valid alternative to quinolone used by some publications in the art.

(10) Nielsen et al.

(11) Kallmann et al.

As to the Nielsen reference, it was cited to show the established status of the nicotinamide in the art for protecting pancreatic islet cells, and particularly under autoimmune condition, and thus justify to use it at a time before or at the same time when the beta cells are extracted from pancreatic tissue. Nielsen et al teach "NA has been proposed to influence several of the putative intracellular molecular events following immune attack on the beta-cells. Animal experiments and early non-blinded experiments in humans have indicated a protective role of this compound against IDDM as well as in cytokine/immune mediated beta-cell destruction"(Column 13).

Kallmann et al was cited to evidence the known association of islet cells, trauma, and nicotinamide.

Claims 216 is rejected under 35 U.S.C. 103(a) as being obvious over *Rayat et al* (Diabetes 1998;47:1406-11), in view of *Brandhorst et al* (Transplant 1999;68:355-61, IDS), and *Boss et al* (US 6,432,710).

Rayat et al teach a method of preparing porcine islet cells as a potential source for transplantation in humans (abstract) comprising harvesting the pancreas from neonatal piglets at 1-3 days, extracting pancreatic islet beta cells, and culturing the islet cells in the presence of nicotinamide and bovine serum albumin (trauma-protecting agent) under sterile condition (free of microbial by including penicillin and streptomycin in the medium, paragraph bridging pages 1406-7). *Rayat et al* go on to teach that beta cells obtained from adult porcine are fragile and difficult to maintain in tissue culture and report the studies in the art regarding use of neonatal and fetal pancreas to obtain beta cells (e.g. 1st paragraph, page 1406, and Discussion). Thus the teachings of *Rayat et al* establish that the prior art recognized the advantages of using fetal and neonatal tissue for obtaining beta islet cells and including nicotinamide in the preparative process.

Rayat et al differ from instant claim in that they use collagenase but not Liberase to extract islet cells; and penicillin and streptomycin but not quinolone as antibiotics.

Brandhorst et al supplement the teaching of *Rayat et al* by disclosing the benefit of substituting collagenase with Liberase. *Brandhorst et al* teach that a barrier for successful islet isolation is the intrinsic fragility of islets during pancreas digestion and

using human Liberase could double the yield of islet cells compared to collagenase (abstract).

Boss et al supplemented the teaching of *Rayat et al* by illustrating that quinoline antibiotics such as ciprofloxacin is useful in preventing mycoplasmal contamination (column 13, line 41-55).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by *Rayat et al* in view of *Brandhorst et al and Boss et al* by substituting collagenase with Liberase in pancreas harvesting and including the ciprofloxacin in culture medium with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because liberase could substantially enhance the yields of islet cells and ciprofloxacin could prevent different type of pathogen infection. Given the choice of digestion enzyme and antibiotics available in the art at the time, these limitations fall within the bound of optimization. Given the success as shown in each of the reference, one would have had a reasonable expectation of success combining the cited teachings. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 217 and 218 are rejected under 35 U.S.C. 103(a) as being obvious over *Rayat et al* (Diabetes 1998;47:1406-11), in view of *Brandhorst et al* (Transplant 1999;68:355-61, IDS), and *Boss et al* (US 6,432,710) as applied to claim 216 above further in view of *Pu et al* (Brit J Pharmacol 1996;118:1072-8).

Claims 217 and 218 are drawn to treating pancreas with an anesthetic agent or a phospholipase A2 inhibitor such as lignocaine as the trauma-protecting agent in the process of preparation. *Rayat et al* in view of *Brandhorst et al* and *Boss et al* fail to teach such.

Pu et al supplement the teachings of *Rayat et al* in view of *Brandhorst et al* and *Boss et al* by a showing that it has been reported in the art that addition of lignocaine in isolated rabbit heart tissue culture could restore the contractility of myocardiocytes after minor traumatic injury (myocardial contusion), and thus lignocaine could be used as a therapeutic agent for tissue recovery from minor trauma (abstract, and § 5). *Pu et al* have extend the observation of lignocaine in protecting heart cells to apply to all tissue recovery from minor trauma, and the trauma due to tissue harvesting and extraction certainly fall within the category of minor trauma. *Pu et al* suggested that although further confirmation study is needed, lignocaine is likely a promising therapeutic intervention (abstract, § 5).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the methods taught by *Rayat et al,* in view of *Brandhorst et al*, *Boss et al* and *Pu et al* by including lignocaine in the pancreas harvesting and extracting process with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because the lignocaine has been proven effective in protecting cells from minor injury. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 221 is rejected under 35 U.S.C. 103(a) as being obvious over *Rayat et al* (Diabetes 1998;47:1406-11), in view of *Brandhorst et al* (Transplant 1999;68:355-61, IDS), and *Maysinger et al* (CA 2,216,055, IDS).

Rayat et al teach a method of preparing porcine islet cells as potential source for transplantation in humans (abstract) comprising harvesting the pancreas from neonatal piglets at 1-3 days, extracting pancreatic islet beta cells, and culturing the islet cells in the presence of nicotinamide and bovine serum albumin (trauma-protecting agent) under sterile condition (free of microbial by including penicillin and streptomycin in the medium, paragraph bridging pages 1406-7). *Rayat et al* go on to teach that beta cells obtained from adult porcine are fragile and difficult to maintain in tissue culture and report the studies in the art regarding use of neonatal and fetal pancreas to obtain beta cells (e.g. 1st paragraph, page 1406, and Discussion). Thus the teachings of *Rayat et al* establish that the prior art recognized the advantages of using fetal and neonatal tissue for obtaining beta islet cells and including nicotinamide in the preparative process.

Rayat et al differ from instant claim in that they use collagenase but not Liberase to extract islet cells; and do not specify use IGF-1 in the isolation/cultivation process.

Brandhorst et al supplement the teaching of *Rayat et al* by disclosing the benefit of substituting collagenase with Liberase. *Brandhorst et al* teach that a barrier for successful islet isolation is the intrinsic fragility of islets during pancreas digestion and using human Liberase could double the yield of islet cells compared to collagenase (abstract).

Maysinger et al supplemented the teaching of *Rayat et al* by illustrating it is well known in the art to use IGF-I in islet cell preparation for transplantation at the time before instant priority date. *Maysinger et al* teach that it is desirable to provide IGF-I in the culture medium of islet cells to prevent cell death (apoptosis) thereby promoting islet cell survival (e.g. page 4).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by *Rayat et al* in view of *Brandhorst et al* and *Maysinger et al* by substituting collagenase with Liberase in pancreas harvesting and including the IGF-1 in culture medium with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because liberase could enhance the yields of islet cells substantially and IGF-I could prevent/reduce islet cell death during the preparation. Given the aforementioned knowledge available in the art at the time, these limitations fall within the bound of optimization. Given the success as shown in each of the references, one would have had a reasonable expectation of success combining the cited teachings. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA

1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 194, 195, 197, 198 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 11, 13, and 14 of U.S. Patent No. 6,146,653.

Applicants elected to defer submission of a terminal disclaimer until such time as the claims are allowed in the present case.

In response, the rejection stands until the filing of a disclaimer.

Claim Objections

Claims 189, 192, 201, 205 stand objected and claims 219, 220 are newly objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Claims 212-215 are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is 571-272-0730. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Dave T. Nguyen** can be reached on 571-272-0731. The **fax** numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

Any inquiry of formal matters can be directed to the patent analyst, **Victor Barlow**, whose telephone number is (571) 272-0506.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Q. JANICE LI, M.D.
PRIMARY EXAMINER

Q. Janice Li, M.D.
Primary Examiner
Art Unit 1633

QJL
October 31, 2005